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CRY1 and *CRY2* genetic variants in seasonality: A longitudinal and cross-sectional study

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ABSTRACT

Cryptochromes are key components of the circadian clocks that generate and maintain seasonal variations. The aim of our study was to analyze the associations of *CRY1* and *CRY2* genetic variants with the problematicity of seasonal variations, and whether the problematicity of seasonal variations changed during the follow-up of 11 years. Altogether 21 *CRY1* and 16 *CRY2* single-nucleotide polymorphisms (SNPs) were genotyped and analyzed in 5910 individuals from a Finnish nationwide population-based sample who had filled in the self-report on the seasonal variations in mood and behavior in the year 2000. In the year 2011, 3356 of these individuals filled in the same self-report on the seasonal variations in mood and behavior. Regression models were used to test whether any of the SNPs associated with the problematicity of seasonal variations or with a change in the problematicity from 2000 to 2011. In the longitudinal analysis, *CRY2* SNP rs61884508 was protective from worsening of problematicity of seasonal variations. In the cross-sectional analysis, *CRY2* SNP rs72902437 showed evidence of association with problematicity of seasonal variations, as did SNP rs1554338 (in the *MAPK8IP1* and downstream of *CRY2*).

1. Introduction

For the majority of the human population, there are fluctuations in mood and behavior across seasons (Kasper et al., 1989). Among individuals having mood disorder these seasonal variations tend to be pronounced (Wehr and Rosenthal, 1989). Seasonal variations characterize the clinical picture of those with the seasonal pattern or seasonal affective disorder (SAD) (Rosenthal et al., 1984b). The winter type of SAD is the most common form (Partonen and Lonnqvist, 1998; Patten et al., 2016). Earlier, we have shown that, of the Finnish general population aged 30 and over, 85% which corresponds to the estimated number of 2,766,037 inhabitants followed a seasonal pattern in mood and behaviors, 38.9% (1,266,531 inhabitants) experienced routine seasonal variations to the extent of threshold-level SAD, and 2.6% (85,615 inhabitants) suffered from these symptoms to the extent equal to SAD (Grimaldi et al., 2009).

Physiological functions and behaviors demonstrate daily and seasonal variations that are generated and maintained by the circadian clocks responding to stimuli from the habitat (Meijer et al., 2007). Within cells on molecular level, cryptochromes guide a range of functions of the circadian clocks (Lamia et al., 2011), and they are necessary for the development of intercellular networks in the master circadian clock in the cells of the suprachiasmatic nucleus (Ono et al., 2013) that produces synchronizing signals throughout the organism (Evans et al., 2015). Environmental light and ambient temperature of the external 24-hour cycle act together to dictate the phase and to entrain circadian clocks (Boothroyd et al., 2007), but the change of seasons tends to challenge their functions (Stoleru et al., 2007). Since most biochemical reactions respond robustly to temperature, it might have been used as the original, universal time-giver to the organism (Buhr et al., 2010), and the evolution of mechanisms to buffer the effects of day-to-day (or season-to-season) changes in ambient temperature expected to favor adaptation (Francois et al., 2012). Concerning day-active animals, transcription of the cryptochrome genes that are key components of the circadian clocks is induced in the evening (Lincoln et al., 2002), and the heat-induced phase shifts of the circadian clock are severely reduced in the cryptochrome loss-of-function mutants (Kaushik et al., 2007). Thus, the cryptochrome proteins regulate the temperature entrainability, and if this were to hold for mammals as well, including humans, then dysfunction of cryptochrome proteins may contribute to the seasonal variations in mood and behavior being experienced as a problem.

Dysfunction of the circadian clocks has been hypothesized to play a role in the etiology of mood disorders (Bunney and Potkin,

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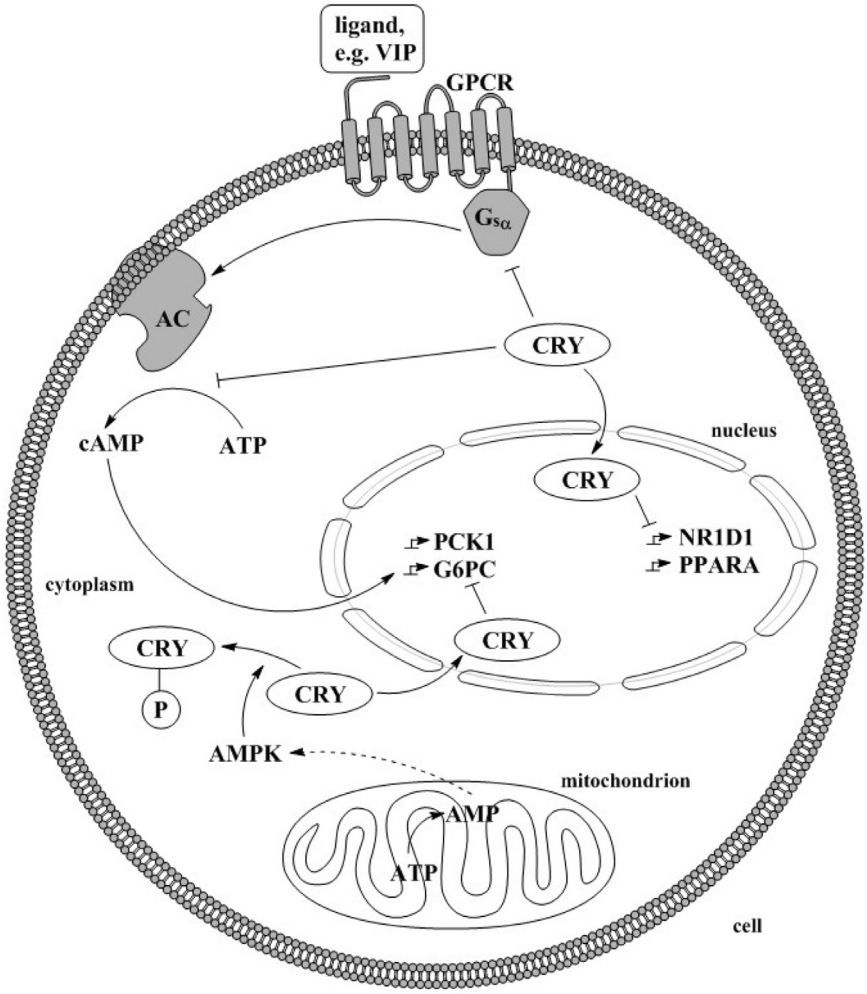

Fig. 1. Schematic of the key functions of cryptochromes in a cell. Cryptochromes (CRY2 and CRY1) are proteins that are repressors in the transcription-translation loops in the core of circadian clocks, and inhibitors of the cyclic adenosine monophosphate signal pathway. In the cytoplasm, CRY2 and CRY1 inhibit both the alpha-subunit of stimulatory guanosine-triphosphate-binding proteins coupled to transmembrane receptors and the activity of adenylyl cyclase. Adenylyl cyclase produces the second messenger cyclic adenosine monophosphate for intracellular signaling. In the nucleus, CRY2 and CRY1 repress the transcription of, e.g., *PCK1*, *G6PC*, *NR1D1* and *PPARA*. *PCK1* is a main control point for the regulation of gluconeogenesis, and *G6PC* encodes a key enzyme in glucose homeostasis. *NR1D1* encodes a ligand-sensitive transcription factor that negatively regulates the expression of core clock proteins, and *PPARA* encodes a key regulator of lipid metabolism for the peroxisomal beta-oxidation pathway of fatty acids and for the propagation of clock information to metabolic pathways. By these actions, CRY2 and CRY1 are involved in the functions of circadian clocks and in the metabolism of glucose and lipids, and they may contribute to mood regulation on daily basis as well as to seasonal variations in mood and behavior. Abbreviations: AC=adenylyl cyclase; AMP=adenosine monophosphate; AMPK=adenosine-monophosphate-activated protein kinase; ATP=adenosine triphosphate; cAMP=cyclic adenosine monophosphate; CRY=cryptochrome; GPCR=G protein–coupled receptor; G6PC=glucose-6-phosphatase, catalytic subunit; $G_{s\alpha}$=stimulatory guanosine-triphosphate-binding protein, alpha subunit; NR1D1=nuclear receptor subfamily 1, group D, member 1; P=phosphorus; PCK1=phosphoenolpyruvate carboxykinase 1 (soluble); PPARA=peroxisome proliferator-activated receptor alpha; VIP=vasointestinal peptide.

2008). Those genes which encode repressors of transcription are thought to be of key importance, since they are essential to the normal function of circadian clocks (Ukai-Tadenuma et al., 2011). Here, the cryptochrome circadian clock 2 (CRY2) and cryptochrome circadian clock 1 (CRY1) proteins are the key repressors in the core of the circadian clock (Dardente et al., 2007; Ozturk et al., 2007; Ye et al., 2011, 2014). However, CRY2 has a key role in balancing the expression of cryptochromes, as it not only acts as a general repressor, but also opposes in specific the actions of CRY1 and inhibits CRY1 from accessing to its targets too early (Anand et al., 2013). See Fig. 1 for a schematic of the key functions of cryptochromes in a cell.

CRY2 has been associated with depressive disorders (Lavebratt et al., 2010; Kovanen et al., 2013), bipolar disorders (Sjoholm et al., 2010), and greater chronicity of depressive symptoms in patients with major depressive or bipolar disorder (Fiedorowicz et al., 2012). On the other hand, *CRY1* has earlier been associated with depression (Soria et al., 2010; Hua et al., 2014) and nominally significant association has been observed with lithium treatment response for bipolar disorder (McCarthy et al., 2011). However, no association with bipolar disorder has been observed (Shi et al., 2008; Nievergelt et al., 2005). Thus, data from the very beginning to date are so far consistent with the hypothesis that CRY2 and CRY1 proteins modulate circadian and emotional responses, and therefore *CRY2* and *CRY1* are highly interesting and relevant target to study the seasonal variations in mood and behavior in humans. Here, we hypothesize that there is a variant of *CRY2* or *CRY1* which increases the odds for seasonal variations in mood and behavior being experienced as a problem.

Cryptochromes may be involved not only in regulation of mood and behavior, but also in that of metabolism of glucose, cholesterol and triglycerides. In a consortium meta-analysis of genome-wide association studies using the Homeostasis Model Assessment indices of insulin resistance and beta-cell function, the A-allele of *CRY2* SNP rs11605924 was found to associate with fasting glucose and beta-cell function, but not to play a major role in type

2 diabetes (Dupuis et al., 2010). Later, only a nominal association of type 2 diabetes was seen with the C-allele of *CRY2* SNP rs2292912, but the finding complemented earlier findings and pointed at the role for *CRY2* in susceptibility to type 2 diabetes (Kelly et al., 2012). Recently, however, these findings were extended by showing that *CRY2* SNP rs11605924 was associated with glucose levels in healthy children, adolescents and adults, the A-allele being identified as a glucose-raising allele (Barker et al., 2011). In addition, the minor alleles of the *CRY2* SNPs rs11605924, rs10838524 and rs7933420 all revealed increases in fasting glucose in a sample of non-diabetic individuals with the family history of type 2 diabetes (Machicao et al., 2016). Furthermore, the A-allele of *CRY2* SNP rs11605924 was confirmed to associate with fasting glucose, and shown to associate with the 2-hour glucose levels after the 75-gram oral glucose tolerance test if administered during the winter, but not if administered in the summer (Renstrom et al., 2015). On the other hand, the minor C-allele of *CRY1* SNP rs2287161 was shown to interact with the level of carbohydrate intake, that is both a susceptibility factor to type 2 diabetes and a characteristic of seasonal affective disorder, to modulate fasting insulin and insulin resistance (Dashti et al., 2014). To our knowledge, there are no earlier data on the associations of *CRY1* or *CRY2* variants with cholesterol levels or those of triglycerides. Here, we hypothesize that there is a variant of *CRY2* or *CRY1* which increases the odds for adverse profiles of glucose, cholesterol or triglycerides metabolism, and that such variant is more frequent among those with problematic seasonal variations in mood and behavior.

Our aim in this prospective study representative of the general adult population aged 30 years and older was to analyze, whether there is any *CRY1 or CRY2* genetic variant, which associates with a change in the problematicity of the seasonal variations during the study period of 11 years, and therefore provides information on the prognosis. Here, we report *CRY2* genetic associations with the problematicity of seasonal variations in mood and behavior, and in a longitudinal analysis, with worsening of the problematicity.

2. Methods

2.1. Subjects

Our sample included 5910 individuals who had given blood samples, taken part to the Munich-Composite International Diagnostic Interview (M-CIDI) (Wittchen et al., 1998) and filled in the self-report on the seasonal variations in mood and behavior during the winter months of the year 2000. Of these 5910 individuals

Table 1
Successfully genotyped *CRY1 and CRY2* SNPs, their allele and genotype frequencies, and Hardy-Weinberg equilibrium *p*-values.

Gene	SNP	BP NCBI36/hg18	A1	A2	MAF	A1A1	A1A2	A2A2	HWE *p*
CRY2	rs7121611	45,864,142	*A*	*T*	0.46	1218 (21.0)	2883 (49.6)	1711 (29.4)	0.96
	rs7121775	45,864,323	*C*	*T*	0.27	384 (6.6)	2326 (40.0)	3100 (53.4)	0.06
	rs61884508	45,864,932	*G*	*T*	0.02	1 (0)	241 (4.1)	5600 (95.9)	0.52
	rs75065406	45,864,942	*T*	*C*	0.04	13 (0.2)	421 (7.2)	5414 (92.6)	0.11
	rs3747548	45,869,013	*A*	*C*	0.00	0	1 (0)	5847 (100)	1.00
	rs10838524	45,870,177	*G*	*A*	0.48	1337 (23.0)	2897 (49.8)	1579 (27.2)	0.92
	rs2292913	45,877,529	*T*	*C*	0.05	18 (0.3)	590 (10.1)	5233 (89.6)	0.70
	rs7945565	45,878,992	*G*	*A*	0.46	1213 (20.9)	2890 (49.8)	1695 (29.2)	0.79
	rs1401419	45,879,739	*G*	*A*	0.46	1211 (20.9)	2909 (50.1)	1681 (29.0)	0.48
	rs72902437	45,882,258	*C*	*T*	0.03	2 (0)	313 (5.4)	5499 (94.6)	0.45
	rs35488012	45,889,228	*G*		0.00	0	0	5854 (100)	1.00
	rs117531403	45,891,332	*C*		0.00	0	0	5848 (100)	1.00
	rs7123390	45,891,418	*A*	*G*	0.29	431 (7.4)	2445 (42.2)	2915 (50.3)	0.01
	rs4755345	45,891,508	*A*	*G*	0.05	18 (0.3)	598 (10.2)	5229 (89.5)	0.80
	rs76545099	45,891,667	*T*		0.00	0	0	5850 (100)	1.00
	rs17787136	45,894,636	*G*	*C*	0.28	409 (7.0)	2385 (41.1)	3014 (51.9)	0.03
	rs10838527	45,903,194	*G*	*A*	0.12	89 (1.5)	1236 (21.2)	4509 (77.3)	0.67
	rs2292910	45,903,613	*A*	*C*	0.34	650 (11.2)	2707 (46.6)	2455 (42.2)	0.02
	rs3824872	45,905,605	*T*	*G*	0.25	372 (6.4)	2173 (37.3)	3276 (56.3)	0.65
	rs1554338	45,906,830	*G*	*A*	0.05	14 (0.2)	528 (9.1)	5289 (90.7)	0.77
CRY1	rs4964513	107,375,758	*C*	*T*	0.12	84 (1.4)	1224 (21.1)	4492 (77.4)	0.95
	rs714359	107,378,845	*A*	*G*	0.22	276 (4.8)	2006 (34.6)	3516 (60.6)	0.67
	rs12821586	107,380,452	*A*	*G*	0.11	72 (1.2)	1138 (19.5)	4629 (79.3)	0.84
	rs2287161	107,381,140	*C*	*G*	0.50	1408 (24.3)	2930 (50.5)	1461 (25.2)	0.43
	rs11113153	107,381,770	*T*	*C*	0.17	178 (3.1)	1624 (28.3)	3946 (68.6)	0.49
	rs8192441	107,385,454	*C*	*A*	0.01	1 (0)	136 (2.3)	5712 (97.7)	0.56
	rs3741892	107,387,163	*C*	*G*	0.49	1395 (24.0)	2937 (50.6)	1477 (25.4)	0.40
	rs10861688	107,394,048	*T*	*C*	0.17	164 (2.8)	1642 (28.2)	4011 (69.0)	0.82
	rs10861695	107,415,073	*A*	*G*	0.49	1385 (24.0)	2901 (50.4)	1474 (25.6)	0.58
	rs10861697	107,419,662	*C*	*G*	0.49	1352 (23.3)	2923 (50.4)	1521 (26.2)	0.48
	rs2078074	107,436,806	*C*	*T*	0.42	1017 (17.7)	2815 (48.9)	1930 (33.5)	0.87
	rs59790130	107,440,303	*T*	*C*	0.06	26 (0.4)	692 (11.8)	5131 (87.7)	0.58
	rs10437895	107,440,824	*C*	*T*	0.49	1398 (24.0)	2936 (50.5)	1482 (25.5)	0.46
	rs10746077	107,441,552	*A*	*G*	0.42	1027 (17.6)	2832 (48.7)	1960 (33.7)	0.96
	rs11613557	107,442,315	*T*	*C*	0.06	26 (0.4)	692 (11.8)	5130 (87.7)	0.58
	rs2888896	107,446,582	*T*	*C*	0.42	1019 (17.6)	2830 (48.8)	1947 (33.6)	0.87
	rs11113179	107,452,785	*T*	*C*	0.08	39 (0.7)	833 (14.3)	4942 (85.0)	0.53
	rs10746083	107,454,152	*T*	*C*	0.49	1391 (23.9)	2941 (50.6)	1481 (25.5)	0.37
	rs4964518	107,466,217	*T*	*C*	0.07	30 (0.5)	778 (13.3)	5027 (86.2)	1.00
	rs7294758	107,467,829	*A*	*T*	0.01	0	97 (1.7)	5758 (98.3)	1.00
	rs17289712	107,468,968	*G*	*A*	0.05	6 (0.1)	524 (9.0)	5308 (90.9)	0.07
	rs10778528	107,473,962	*G*	*T*	0.48	1358 (23.3)	2926 (50.3)	1533 (26.4)	0.62

Abbreviations: BP; Base pair position based on NCBI36/hg18 build. A1; Minor allele. A2; Major allele. MAF; Minor allele frequency. A1A1, A1A2, A2A2; genotype counts and frequencies (%). HWE; Hardy-Weinberg equilibrium.

3356 filled in the self-report on the seasonal variations in mood and behavior again during the winter months of the year 2011. The sample is part of the national Health 2000 survey (Aromaa and Koskinen, 2004) of Finnish population aged 30 years and older (n=8028) and its follow-up survey in the year 2011. The study was approved by the ethics committees of the National Public Health Institute and the Helsinki and Uusimaa Hospital District. The study was carried out in accordance with the principles of the Declaration of Helsinki and its amendments. All participants provided a written informed consent.

2.2. Phenotypes

The participants filled in a questionnaire of lifetime seasonal variations in mood and behavior adapted from the Seasonal Pattern Assessment Questionnaire (SPAQ) (Rosenthal et al., 1984a). The six items of sleep duration, social activity, mood, weight, appetite, and energy level had been scored from 0 to 3 (none, slight, moderate, or marked variation) rather than from 0 to 4 (none, slight, moderate, marked, or extremely marked variation). The psychometric properties of this modified questionnaire have been reported to be good (Rintamaki et al., 2008). The participants were also asked to what degree seasonal variations if any were a problem (no variations, no problem, and mild, moderate, marked, or severe problem).

For the purpose of the cross-sectional analysis, a variable was formed as follows: no seasonal variations (all six items no variation and problem degree no variations), non-problematic seasonal variations (at least 1 item with variation and variation is no problem), or problematic seasonal variations (at least 1 item with variation and variation is a problem). For the purpose of the longitudinal analysis, the individual change in the aforementioned variable was computed: equal (n=1625), worse (n=928), or better (n=428). Supplementary material 1 shows the computation of the variables for the cross-sectional (Supplementary Table 1) and longitudinal analysis (Supplementary Table 2).

2.3. Health examination

Height and weight were measured, and the body-mass index (BMI) was calculated. Body circumference measurements were taken using a regular, flexible tailor's measuring tape at waist and hip level in line with recommendations for anthropometric measurements in population studies.

Current instructions of the Finnish Hypertension Society working group were followed for blood pressure measurements that were taken after calibration using a standard mercury manometer (Mercuro 300; Speidel & Keller, Jungingen, Germany). The measurement was repeated two minutes after the first one, and the average of the two was used for analysis.

2.4. Laboratory analyses

As part of the health examination, venous blood samples were drawn and laboratory measures included in the analysis were total cholesterol (CHOD PAP, Olympus System Reagent, Freiburg, Germany), high-density lipoprotein (HDL) cholesterol (HDL-C Plus, Roche Diagnostics, Penzberg, Germany), triglycerides (GPO PAP, Olympus System Reagent, Freiburg, Germany), and plasma glucose (Hexokinase, Olympus System Reagent, Freiburg, Germany). LDL cholesterol was calculated with the Friedewald formula (Friedewald et al., 1972). All these samples were determined enzymatically with a clinical chemistry analyzer (Olympus AU400, Hamburg, Germany) at the Social Insurance Institution (Kela), Research and Development Unit, Finland. Plasma insulin concentrations were determined using a radioimmunoassay (Phadeseph Insulin RIA, Pharmacia, Uppsala, Sweden). Homeostasis Model Assessment indices of insulin resistance (HOMA-IR) and beta-cell function (HOMA-B) were calculated according to the following formula: HOMA-IR=fasting glucose (mmol/L) × fasting insulin (mU/L) divided by 22.5 and HOMA-B=20 × [(fasting insulin) divided by (fasting glucose minus 3.5)] (Matthews et al., 1985). Serum 25-hydroxyvitamin D_3 concentrations were determined using a radioimmunoassay (DiaSorin, Saluggia, Italy). The laboratory took part in the External Quality Assessment schemes (Labquality, Helsinki, Finland), the accuracy for the lipid determinations was also calculated by the Lipids and lipoproteins program, and the quality of the results of the series of all the analyses was ascertained.

2.5. Gene and SNP selection

CRY1 and CRY2 single-nucleotide polymorphism (SNP) selection was based on HapMap phase 3 data (http://www.hapmap.org/) and tagging was done using the Tagger program in the Haploview 4.1 software (Barrett et al., 2005). The linkage disequilibrium (LD), within the gene and 10 kb of their 5′ and 3′ flanking regions, i.e., 122 kb for *CRY1* (chr12:105 899–106 021 kb, NCBI36/hg18 assembly), and 56 kb for *CRY2* (chr11:45,815–45,871 kb), was used to select tag SNPs capturing most of the genetic variation. The aim was to capture all the SNPs having a minor allele frequency (MAF) of $>5\%$ in the European population (CEU and TSI) in the HapMap database. The pair-wise r^2 was set to ≥ 0.9 in order to select a tag SNP among the SNPs that were in LD. Ten out of 21 *CRY1* and ten out of 34 *CRY2* SNPs fulfilled the criterion and were all successfully included in the genotyping multiplex. In addition to the aforementioned tag-SNPs, 22 potentially functional variants in *CRY1* (12 variants) and *CRY2* (10 variants) were included in

Table 2
General characteristics of the participants (n=5739) in the year 2000.

Characteristic	*n*	%	
Gender			
Female	3195	56	
Male	2544	44	
Seasonal variation in sleep duration			
Cases	4178	73.88	
Controls	1477	26.12	
Seasonal variation in social activity			
Cases	3980	71.72	
Controls	1569	28.28	
Seasonal variation in mood			
Cases	4263	76.03	
Controls	1344	23.97	
Seasonal variation in weight			
Cases	2771	49.47	
Controls	2830	50.53	
Seasonal variation in appetite			
Cases	2404	42.68	
Controls	3228	57.32	
Seasonal variation in energy level			
Cases	4235	75.34	
Controls	1386	24.66	
Seasonal variation as a problem			
No variation	361	7.06	
Non-problematic variation	3824	74.75	
Problematic variation	931	18.20	
	n	**mean**	***s.d.***
Age, years	5739	53.13	15.04
BMI, kg/m^2	5722	26.97	4.70
GSS, score points	5469	5.04	3.07

Abbreviations: BMI; body mass index. GSS; global seasonality score.

Table 3
Baseline characteristics of the participants with problematic, non-problematic and no variation.

	problematic variation			non-problematic variation			no variation			problematic vs. non-problematic		problematic vs. no variation	
	n	mean	%/SD	n	mean	%/SD	n	mean	%/SD	χ^2/ t	p	χ^2/t	p
Male gender	365		39.21	1675		43.80	201		55.68	6.27	0.01	28.01	0.0000001
Female gender	566		60.79	2149		56.20	160		44.32				
Age	931	53.55	15.07	3824	51.43	14.27	361	55.42	16.46	−3.89	0.0001	1.87	0.06
Glucose	931	5.58	1.38	3822	5.52	1.13	361	5.66	1.36	−1.27	0.20	0.95	0.34
Total cholesterol	931	5.93	1.16	3822	5.91	1.09	361	6.00	1.13	−0.54	0.59	0.96	0.34
HDL cholesterol	931	1.33	0.38	3822	1.34	0.38	361	1.29	0.37	1.11	0.27	−1.69	0.09
LDL cholesterol	928	3.66	1.11	3805	3.70	1.03	360	3.80	1.10	0.87	0.39	1.96	0.05
Triglycerides	931	1.69	1.23	3822	1.56	0.98	361	1.66	1.07	−2.92	0.004	−0.37	0.71
25-hydroxyvitamin D3	880	44.92	16.55	3672	45.57	16.85	342	43.58	16.97	1.03	0.30	−1.25	0.21
Insulin	905	9.11	9.06	3762	9.71	14.37	348	9.41	7.63	−1.59	0.11	−0.61	0.54
Weight	930	77.00	16.20	3819	76.15	15.33	360	75.97	15.22	−1.44	0.15	−1.07	0.29
Waist circumference	922	93.90	14.11	3792	92.03	13.06	354	93.21	13.51	−3.67	0.0003	−0.81	0.42
BMI	930	27.45	5.01	3818	26.77	4.61	360	26.63	4.49	−3.74	0.0002	−2.85	0.004
GSS	874	8.00	2.87	3734	5.07	2.47	361	0.00	0.00	−27.82	< 2.2e-16	−82.42	< 2.2e-16
Systolic blood pressure	925	133.51	21.52	3816	134.11	21.02	361	136.06	20.36	0.76	0.45	1.98	0.05
Diastolic blood pressure	923	81.33	11.48	3814	81.70	11.24	361	81.81	10.63	0.88	0.38	0.71	0.48
HOMA-IR	905	2.68	4.32	3760	2.46	6.31	348	2.58	3.17	−1.26	0.21	−0.44	0.66
HOMA-B	903	95.47	69.71	3755	94.37	159.25	347	87.12	53.28	−0.32	0.75	−2.27	0.02
GHQ	908	3.89	3.95	3787	1.49	2.48	355	0.86	2.04	−17.50	< 2.2e-16	−17.82	< 2.2e-16
MBI	485	1.82	1.11	2421	1.06	0.81	175	0.80	0.78	−14.33	< 2.2e-16	−13.10	< 2.2e-16
Hours of sleep	891	7.47	1.36	3685	7.46	1.05	343	7.50	1.33	−0.21	0.84	0.34	0.73
Hip circumference	921	102.86	10.29	3792	101.40	9.30	354	100.89	9.46	−3.93	0.0001	−3.25	0.001

HDL, high-density lipoprotein.
LDL, low-density lipoprotein.
BMI, body-mass index.
GSS, global seasonality score.
HOMA-IR, insulin resistance index.
HOMA-B, beta-cell function index.

the genotyping multiplexes. These additional SNPs were selected using Pupasuite (Conde et al., 2006), Variowatch (Cheng et al., 2012) and dbSMR (Hariharan et al., 2009) databases. See Table 1 for the altogether 42 selected SNPs.

2.6. Genotyping

Genomic DNA was isolated from whole blood according to standard procedures. The SNPs were genotyped at the Institute for Molecular Medicine Finland, Technology Centre, University of Helsinki using the MassARRAY iPLEX method (Sequenom, San Diego, CA, USA) (Jurinke et al., 2002), with excellent success (> 95%) and accuracy (100%) rates (Lahermo et al., 2006). For quality control purposes, positive (CEPH) and negative water controls were included in each 384-plate. Genotyping was performed blind to phenotypic information.

171 of 5910 individuals were excluded due to a high missing genotype rate (i.e. > 0.1). The total genotyping rate in the remaining individuals was 0.999. Three *CRY2* SNPs turned out to be non-polymorphic (rs35488012, rs117531403, rs76545099). Two SNPs were excluded from the analyses because their minor allele frequency was less than 0.01 (*CRY2* rs3747548, *CRY1* rs7294758). Finally, there were 5739 individuals and 37 SNPs for the statistical analyses.

2.7. Statistical analyses

Statistical analyses were performed using logistic regression and additive genetic model controlling for age and sex with PLINK software v1.07 (Purcell et al., 2007). Subjects having problematic seasonal variations were compared to subjects with non-problematic seasonal variations, and to subjects with no seasonal variation. A change in the seasonal variations for the better, and a change for the worse were compared to no change. Haplotype blocks were defined using Haploview software (Barrett et al., 2005) and the confidence interval algorithm. Only haplotypes with more than 5% frequency are reported. In order to corrected for the multiple SNPs within a gene, the gene-based analysis was conducted using the set-based test in PLINK software with the default settings and 10,000 permutations, yielding the empirical p-values.

3. Results

In Table 1, the genotypes, allele frequencies and the Hardy-Weinberg equilibrium p-values are shown for all the 42 SNPs that were successfully genotyped in this study. The general characteristics of all the participants are presented in Table 2 and for the three groups in Table 3. The group with problematic variation had the highest BMI and hip circumference. The group with non-problematic variation had lowest triglycerides and waist circumference. The group with no variation had highest LDL cholesterol and systolic blood pressure and lowest HOMA-IR. The Haploview analysis yielded three haplotype blocks for *CRY1* and one haplotype block for *CRY2* gene (Figs. 2 and 3) which had 11 and five common (> 5% frequency) haplotypes, respectively.

3.1. Cross-sectional analysis

CRY1 SNP rs714359 (*A* allele, *OR* = 1.33, 95% *CI* 1.07–1.66, $p = 0.01$; see Table 4) showed nominally significant association with the problematicity of seasonal variations (problematic vs. no variation), and rs714359 (*A* allele, *OR* = 1.14, 95% *CI* 1.01–1.29, $p = 0.03$) and rs2287161 (*C* allele, *OR* = 0.90, 95% *CI* 0.81–1.00, $p = 0.05$) with the problematicity of seasonal variations (problematic vs. non-problematic). The set-based analysis did not support

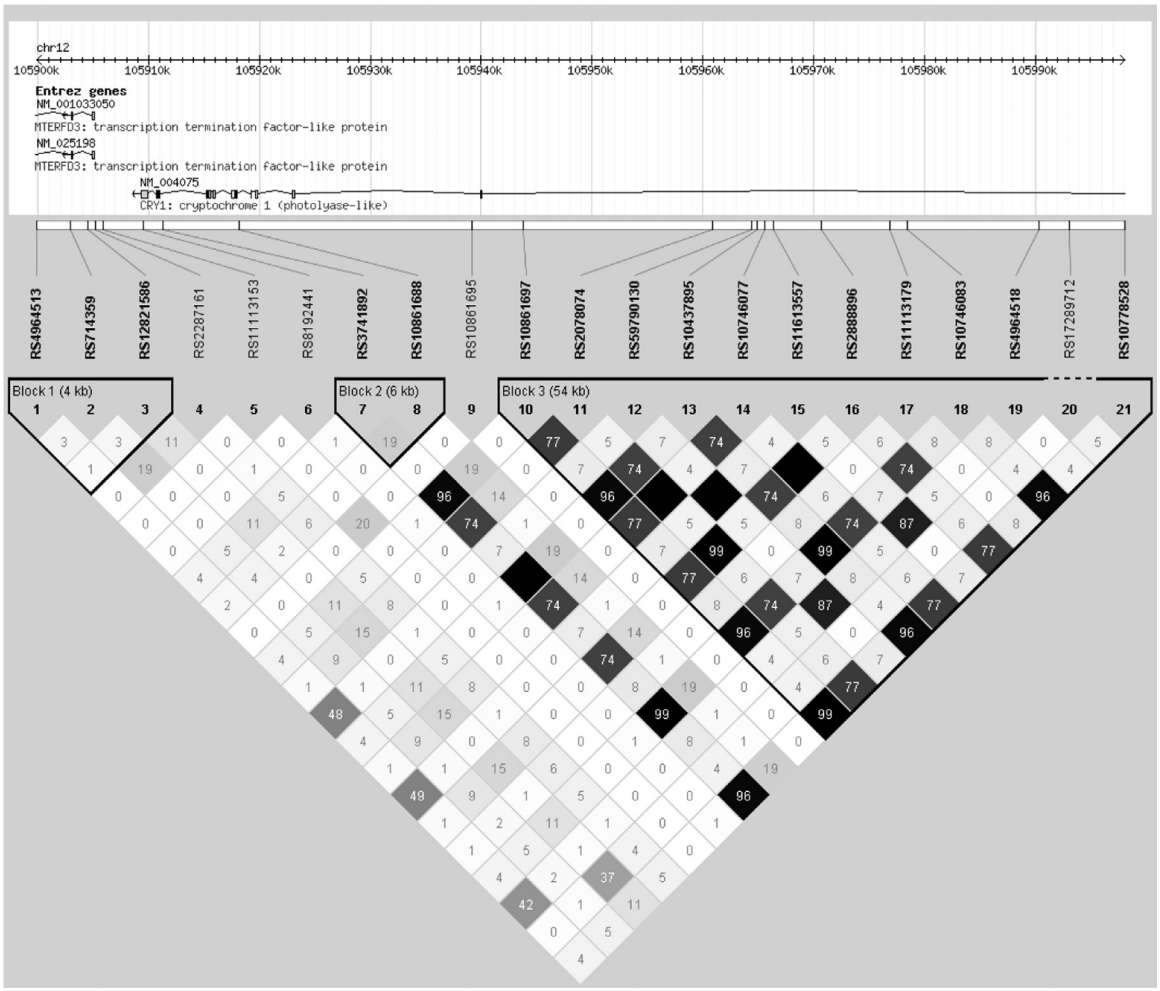

Fig. 2. The analyzed *CRY1* SNPs, their location and the haplotype block structure constructed using the Haploview program showing r^2 values.

these associations (Table 5). However, the *CRY1* haplotype *TAG* including rs714359 showed nominally significant association with the problematicity of seasonal variations (problematic vs. no variation, *OR*=1.33, *p*=0.01; and problematic vs. non-problematic, *OR*=1.14, *p*=0.03; see Table 6). All the SNP and haplotype association analysis results are shown in Supplementary material 2 (Supplementary Table 3 for SNP association results and Supplementary Table 4 for haplotype association results).

CRY2 SNPs rs1554338 (*G* allele, *OR*=0.67, *95% CI* 0.51–0.87, *p*=0.0035) and rs72902437 (*C* allele, *OR*=1.45, *95% CI* 1.08–1.93, *p*=0.01; see Table 4) showed nominally significant association with the problematicity of seasonal variations (problematic variation vs. non-problematic variation). The set-based analysis supported the association of the two SNPs with the problematicity (empirical set-based *p*=0.03; see Table 5). The *CRY2* haplotype *TTTCACAATGGCACT* (*OR*=0.77, *p*=0.03; see Table 6) was also associated with the problematicity of seasonal variations (problematic variation vs. non-problematic variation).

3.2. Longitudinal analysis

CRY2 SNP rs61884508 (*G* allele, *OR*=0.52, *95% CI* 0.33–0.82, *p*=0.004, *q*=0.14; see Table 3) was associated with worsening of the problematicity of seasonal variations during the follow-up. The set-based analysis supported the SNP association (empirical set-based *p*=0.02; see Table 5).

3.3. Additional analysis

For the aforementioned five SNPs, the results from their associations with the laboratory measurements are given in Supplementary material 3. Among those with problematic seasonal variations, the AA-genotypes of *CRY1* SNP rs714359 had lower HDL cholesterol levels, higher insulin levels, and greater HOMA-IR and HOMA-B indices than GG-genotypes, the GA genotypes being intermediate. Concerning the *CRY1* SNP rs2287161, among those with no seasonal variation the CG-genotypes had lower HDL cholesterol levels than CC-genotypes, and among those with non-problematic seasonal variations the GG-genotypes had lower HDL cholesterol levels than CG-genotypes.

The TT-genotypes, as compared with the CT-genotypes, of *CRY2* SNP rs72902437 had greater HOMA-B indices among those with non-problematic seasonal variations, and higher systolic and diastolic blood pressures among those with no seasonal variation. Concerning the *CRY2* SNP rs1554338, the GG-genotypes had higher total and LDL cholesterol levels and lower HDL cholesterol levels than the AA-genotypes among those with non-problematic seasonal variations.

Among those with worsening of the problematicity of seasonal variations, the TT-genotype carriers, as compared with the GT-genotype carriers, of *CRY2* SNP rs61884508 had higher levels of triglycerides at the baseline.

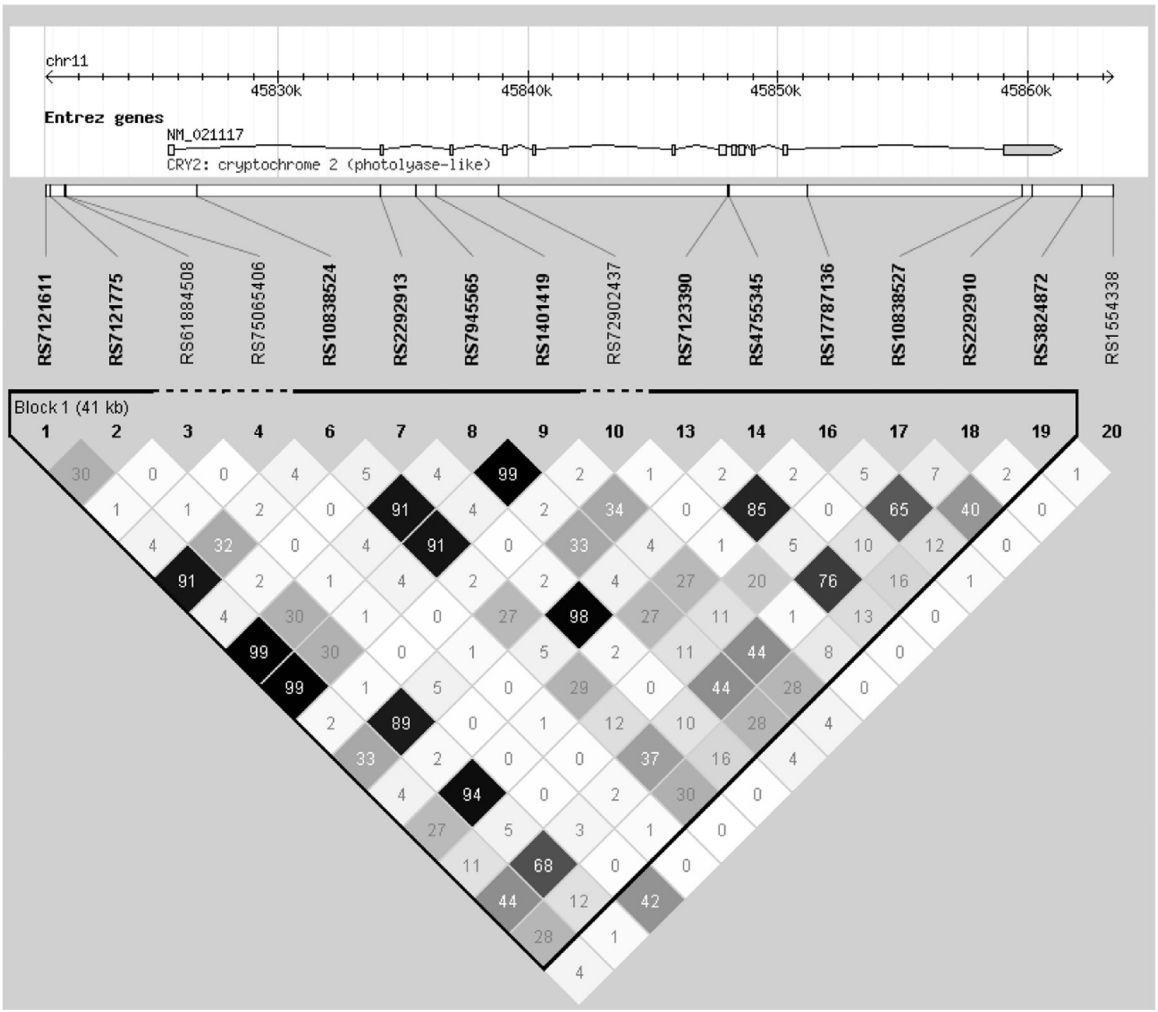

Fig. 3. The analyzed *CRY2* SNPs, their location and the haplotype block structure constructed using the Haploview program showing r^2 values.

Table 4
Longitudinal and cross-sectional nominally significant ($p < 0.05$) *CRY1 and CRY2* SNP association results.

Gene	Phenotype	SNP	A1	*n*	*OR*	*L95*	*U95*	*p*
CRY1	Problematic vs. no variation	rs714359	*A*	1289	1.33	1.07	1.66	0.01
	Problematic vs. non-problematic	rs714359	*A*	4746	1.14	1.01	1.29	0.03
	Problematic vs. non-problematic	rs2287161	*C*	4732	0.90	0.81	1.00	0.05
CRY2	Problematic vs. non-problematic	rs1554338	*G*	4752	0.67	0.51	0.87	0.003
	Problematic vs. non-problematic	rs72902437	*C*	4746	1.45	1.08	1.93	0.01
	Worse	rs61884508	*G*	2552	0.52	0.33	0.82	0.004

Abbreviations: A1; Tested allele (minor allele). N; Number of genotypes for the phenotype. OR; Odds ratio. L95, U95; Lower and upper bounds of 95% confidence interval for odds ratio.

Table 5
Results of the set-based analysis.

SET	Phenotype	NSNP	NSIG	NSIGLD	EMP	SNPs
CRY1	Problematic vs. no variation	21	1	1	0.07	rs714359
	Problematic vs. non-problematic	21	2	2	0.31	rs714359| rs2287161
	Better	21	0	0	1.00	–
	Worse	21	0	0	1.00	–
CRY2	Problematic vs. no variation	16	0	0	1.00	–
	Problematic vs. non-problematic	16	2	2	0.03	rs1554338| rs72902437
	Better	16	0	0	1.00	–
	Worse	16	1	1	0.02	rs61884508

Abbreviations: NSNP; Number of SNPs in the set. NSIG; Number of SNPs with $p < 0.05$. NSIGLD; Number of significant SNPs also passing LD-criterion ($r^2 > 0.5$). EMP; Empirical set-based *p*-value. SNPs; List of SNPs in the set.

4. Discussion

In the longitudinal analysis, we found evidence that carriers of the *CRY2* SNP rs61884508 G-allele had the decreased odds for the worsening of the seasonal variations in mood and behavior as a problem during the 11-year follow-up. In addition, in among the participants that had worsening of the seasonal variations, the triglycerides levels were associated with the *CRY2* SNP rs61884508, the carriers of GT-genotype having lower levels of triglycerides than the carriers of TT-genotype. The *CRY2* SNP rs61884508 is located upstream of *CRY2* gene and was selected to be genotyped because it is located within a putative transcription factor binding site, and it could thus have a role in transcriptional regulation.

In the cross-sectional analysis, we found that the SNP

Table 6
Longitudinal and cross-sectional nominally significant *CRY1 and CRY2* haplotype association results.

Gene	Phenotype	SNP1	SNP2	Haplotype	*F*	*OR*	*p*
CRY1	Problematic vs. no variation	rs4964513	rs12821586	TAG	0.22	1.33	0.01
	Problematic vs. non-problematic	rs4964513	rs12821586	TAG	0.22	1.14	0.03
CRY2	Problematic vs. non-problematic	rs7121611	rs3824872	TTTCACAATGGCACT	0.06	0.77	0.03

Abbreviations: SNP1; SNP ID of the first SNP (5′). SNP2; SNP ID of the last SNP (3′). OR; Odds ratio. F; frequency of the haplotype.

rs1554338 G-allele protected and *CRY2* SNP rs72902437 C-allele predisposed to more severe seasonal variations, i.e., those being problematic vs. non-problematic to the individual. Earlier, the SNP rs1554338 G-allele has been associated with having the seasonal pattern in bipolar disorder (Geoffroy et al., 2015) and nominally ($p=0.031$, not holding after multiple correction) with bipolar I disorder. Here, we found that the GG-genotype associated with both higher total and higher LDL cholesterol levels but lower HDL cholesterol levels compared to AA-genotype, indicating an unfavorable circulating lipids profile, and that it was seen only among those with non-problematic seasonal variations. Intriguingly, the SNP rs1554338 is located in the upstream of *MAPK8IP1* (downstream of *CRY2*). The *MAPK8IP1* gene is indicated in the pancreatic beta-cell function (Waeber et al., 2000), and its scaffolding protein MAPK8IP1 (mitogen-activated protein kinase 8 interacting protein 1) is a key regulator of autophagosome transport in neurons (Fu and Holzbaur, 2014) and has a role in protection of dopaminergic neurons and levels of catecholamines in the striatum (Xia et al., 2001).

We also found that if there were seasonal variations in mood and behavior but they were not a problem, the *CRY2* SNP rs72902437 CT-genotype was associated with a lower HOMA-B index, or a worse beta-cell function compared to TT-genotype, indicating an increased diabetes risk. In contrast, among those with no seasonal variation, systolic and diastolic blood pressures were lower in the carriers of the *CRY2* SNP rs72902437 CT-genotype compared to TT-genotype, indicating a decreased hypertension risk.

The *A*-allele of *CRY2* SNP rs10838524 that was earlier associated with greater chronicity of depressive symptoms in patients with major depressive or bipolar disorder (Fiedorowicz et al., 2012) did not associate with seasonality in our study. However, the A-allele of the *CRY2* SNP rs10838524 was part of TTTCACAATGGCACT haplotype that protected from seasonal variations being problematic in our cross-sectional analysis.

The *CRY1* SNP rs714359 was indicated to influence not only HDL cholesterol levels, but also insulin levels and beyond, as it was involved in insulin resistance and beta-cell function as well. Intriguingly, this influence was seen only among those with problematic seasonal variations. These findings are well in agreement with the earlier report of the influence of the *CRY1* SNP rs2287161 had on fasting insulin and insulin resistance (Dashti et al., 2014).

Our study has some strengths and limitations. Our dataset was rather big and derived from a nationwide representative sample of the general adult population aged 30 years and over. In addition, the cryptochrome genes were well covered. We report here, for the first time, longitudinal data on the influence of *CRY2* genetic variants on the seasonal variations in mood and behavior experienced as a problem. Since problematic seasonal symptoms of mood and behavior are common on population level, our findings might help early identification of individuals who will have worsening of these symptoms.

On the other hand, weaknesses of our study are that the assessment of seasonal variations in mood and behavior was based on the self-report only, and that some participants were lost in the follow-up. In addition, the associated SNPs and haplotype were rather rare. Therefore, replication in another independent sample is needed to confirm our findings, since the minor allele frequency is known to affect the likelihood of a false positive result.

In conclusion, this association analysis has demonstrated an effect of *CRY2* genetic variants in the problematic seasonal variations, and more importantly, with worsening of these seasonal variations as a problem in a longitudinal analysis.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.psychres.2016.05.044.

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